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TITLE: "The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation"

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT The overall goal for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The Consortium has thus assembled three complimentary, multidisciplinary research projects from Johns Hopkins, Massachusetts General Hospital and University of Pittsburgh. Each of the individual projects has made significant progress during this reporting period. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work. The group has met all Major Tasks for Year 1, in particular we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders.					
15. SUBJECT TERMS Vascularized Composite Allotransplantation, Immunoregulation, Tolerance Rejection, Ischemia Reperfusion Cell based Therapy, Large animal models, Allograft, Hand Transplantation ,Face Transplantation					
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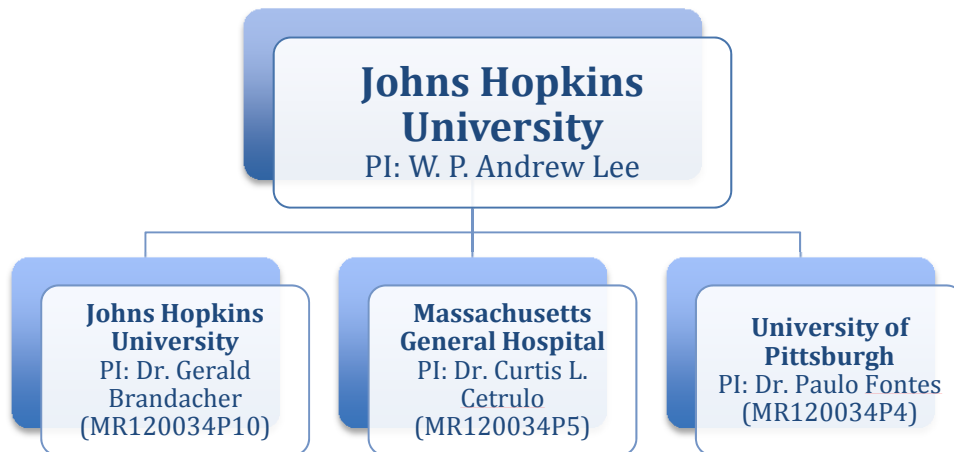
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1. INTRODUCTION

Restorative Transplantation has emerged as a new modality to restore both function and form following devastating injuries to the face and upper extremities in a way not previously possible. Despite initial success, great challenges remain in ameliorating long-term immunosuppression, understanding acute and chronic rejection, and optimizing immune monitoring and perioperative protocols. As the field of Restorative Transplantation matures, significant opportunities are emerging for transplant researchers and clinicians to capitalize on the unique features of VCA, glean from advances and experience in solid organ transplantation (SOT), and achieve genuine progress in transplant outcome and patient safety. **The Johns Hopkins RTR Consortium** has thus *assembled some of the world's most renowned scientists, researchers, and surgeons in vascularized composite allotransplantation (VCA) research to address some of the most relevant and pressing research areas in reconstructive transplantation.*

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The **central hypothesis** is that the maturing field of Restorative Transplantation will benefit the most from the establishment of a multi-institutional, multi-disciplinary collaborative consortium that builds on knowledge and experience derived from the study of SOT to address the unique challenges and opportunities presented in this new field.



2. KEYWORDS

Vascularized Composite Allotransplantation
Immunoregulation
Tolerance
Rejection
Ischemia Reperfusion
Cell based Therapy
Large animal models
Allograft
Hand Transplantation
Face Transplantation

3. ACCOMPLISHMENTS

The Initiating Site has met all Major Tasks for Year 1 as outlined in the Statement of Work. In particular, we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders.

The accomplishments for each of the individual projects are outlined below:

Johns Hopkins University (MR120034P10)

The group obtained approval for the proposed project from both the Institutional Animal Care and Use Committee (IACUC) at Johns Hopkins University as well as the Animal Care and Use Review Office (ACURO) of the Department of Defense.

During year one of this project a non-myeeloablative induction regimen was successfully established consisting of 100cGy total body irradiation (TBI) plus 700cGy thymic irradiation. This treatment protocol was subsequently employed *in vivo* in an immunologically stringent (full class I and class II SLA mismatch) swine heterotopic hind limb allotransplantation model. We have demonstrated that combining this induction regimen with high dose tacrolimus (10-20 ng/mL) maintenance therapy postoperatively successfully prevents rejection. However, as hypothesized, high dose tacrolimus treatment results in clinical complications; one of the primary motivations for this study. Furthermore, we have shown that low dose tacrolimus (4-6 ng/mL) monotherapy postoperatively is not adequate for preventing rejection. These preliminary results again represent a need for adjunct agents such as costimulatory blockade with belatacept to prevent rejection in the setting of post transplant immunosuppression (CNI) minimization.

Massachusetts General Hospital (MR120034P5)

During the first year of this award, effort has been directed towards the first objective: optimization of the delayed tolerance induction protocol for vascularized composite allotransplantation in a non-human primate model.

- Submission and approval of protocols by IACUC and ACURO
- Establishment of screening/selection protocol for optimal donor-recipient pairs of nonhuman primates (ABO blood type compatibility, donor marker expression (H38) for chimerism analysis, MHC typing)
- Commencement of *in vivo* transplantation studies
- Characterisation of donor bone marrow product to be used for induction of chimerism
- Optimization of protocols for *in vitro* analysis of circulating and VCA skin-resident leukocytes

University of Pittsburgh (MR120034P4)

The group has developed a new device to optimize subnormothermic MP in vascularized composite allotransplantation (VCA) by modifying our original Liver Assist Device from Organ Assist, Groningen, Netherlands. The device for VCA as used in the current study incorporates our proprietary HBOC solution to achieve an extended duration of ex-vivo MP (over 14 hours).

The large animal surgical procedures as proposed on this project are near completion (e.g. all ex-vivo experiments and 6/8 in-vivo experiments), allowing for adequate time for correlation of ex vivo and in vivo data, analysis for statistical significance and interpretation of clinically relevant outcomes as outlined in our original application. Key research accomplishments include:

- Successful development of a pre-clinical large animal model for VCA
- Successful development of the RAM graft as a reliable VCA model for I/R injuries
- Successful development of a new MP device for VCA perfusion ex-vivo
- Successful implantation of the heterotopic (cervical) RAM grafts in all surgical experiments.
- Successful implementation of the MP/HBOC method for VCA preservation based on the initial clinical results.

a. What were the major goals of the project?

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners.

b. What was accomplished under these goals?

Each of the individual projects has made significant progress as detailed above. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work.

- c. **What opportunities for training and professional development has the project provided?**

Nothing to Report.

- d. **How were the results disseminated to communities of interest?**

Nothing to Report

- e. **What do you plan to do during the next reporting period to accomplish the goals?**

We will continue our coordinated efforts and increase the frequency of project leader conference calls to ensure timely completion of the tasks as outlined in the statement of work.

4. IMPACT:

- a. **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report

- b. **What was the impact on other disciplines?**

Nothing to report

- c. **What was the impact on technology transfer?**

Nothing to report

- d. **What was the impact on society beyond science and technology?**

Nothing to report

CHANGES/PROBLEMS:

- a. **Changes in approach and reasons for change**

Nothing to report.

- b. **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to report.

- c. **Changes that had a significant impact on expenditures**

Nothing to report.

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

d. Significant changes in use or care of human subjects

Nothing to report.

e. Significant changes in use or care of vertebrate animals.

Nothing to report.

f. Significant changes in use of biohazards and/or select agents

Nothing to report.

5. PRODUCTS

Nothing to report.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: W. P. Andrew Lee

Project Role: Principal Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Gerald Brandacher

Project Role: Co-Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Rochelle Smith

Project Role: Assistant Grant Administrator

Nearest Person Month Worked: 40% (4.8 months)

Contribution to Project: Rochelle Smith drafts reminder emails to send to each site prior to report submission deadlines, coordinates with the PIs to obtain updated information, maintains financial records, and oversees project progress with the Scientific Director and PI.

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

c. Partnering Organization

Johns Hopkins University (MR120034P10)

Gerald Brandacher, MD
Johns Hopkins University
Baltimore, Maryland

Massachusetts General Hospital (MR120034P5)

Curtis L. Cetrulo, MD
Massachusetts General Hospital
Boston, Massachusetts

University of Pittsburgh (MR120034P4)

Paulo Fontes, MD
University of Pittsburgh
Pittsburgh, PA

d. SPECIAL REPORTING REQUIREMENTS

a. **QUAD CHARTS:** Attached.

e. APPENDICES

Nothing to Report.

The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation

MR120034, Restorative Transplantation Research

Award Number: W81XWH-13-2-0059

PI: W. P. Andrew Lee, M.D.

Org: Johns Hopkins University, School of Medicine Award Amount: \$286,298

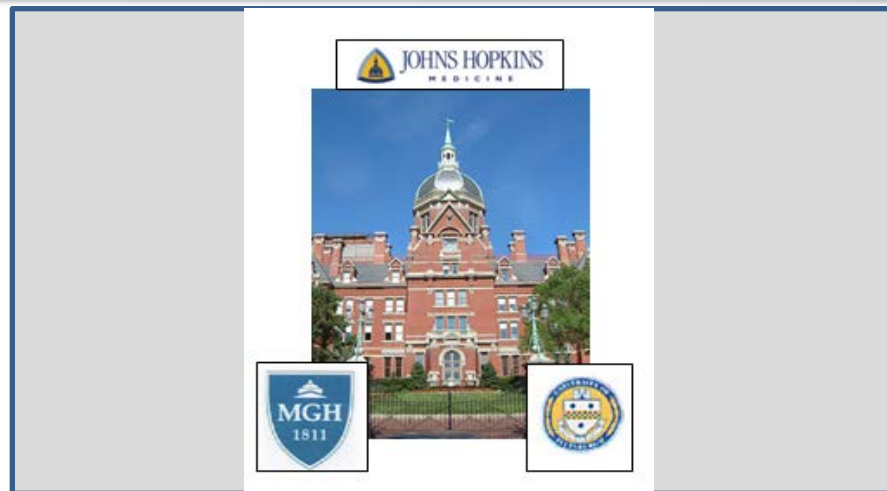


Study/Product Aim(s)

- Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.

Approach

The purpose of this administrative core is to coordinate the efforts of the collaborating sites in order to ensure timely meeting of project aims and milestones while facilitating site communications with the sponsor.



Accomplishment: Implementation of Departmental Clinical Research Core and basic sciences support to enable intra- and inter-institutional research collaborations and perform grant management for both commercial and federal sponsors.

Timeline and Cost

Activities	CY	14	15	16
Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation		<div style="width: 100%; height: 10px; background-color: #92d050;"></div>		
Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation			<div style="width: 100%; height: 10px; background-color: #92d050;"></div>	
Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.				<div style="width: 100%; height: 10px; background-color: #92d050;"></div>
Estimated Budget (\$K)		\$93,790	\$95,558	\$96,950

Goals/Milestones

CY14 Goals

- ☒ Collect & Review Consortium Quarterly Reports
- ☐ Conference Calls with Consortium Sites
- ☒ Milestone: Local IRB/IACUC Approval & HRPO/ACURO Approval

CY15 Goals

- ☐ Collect & Review Consortium Quarterly Reports
- ☐ Conference Calls with Consortium Sites
- ☐ Milestone: Local IRB/IACUC Continuing Review Approval
- ☐ Milestone: HRPO/ACURO Continuing Review Approval

CY16 Goals

- ☐ Collect & Review Consortium Quarterly Reports
- ☐ Conference Calls with Consortium Sites
- ☐ Complete and submit final Consortium Report to Sponsor
- ☐ Milestone: Local IRB/IACUC Continuing Review Approval
- ☐ Milestone: HRPO/ACURO Continuing Review Approval

Comments/Challenges/Issues/Concerns

- N/A

Budget Expenditure to Date

Projected Expenditure: N/A

Actual Expenditure: \$86,628.95

Updated: October 14, 2014